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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/015,469	01/29/98	KINGSTON	H 04945000095

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EXAMINER	
SODERQUIST, A	
ART UNIT	PAPER NUMBER
1743	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 09/015,469	Applicant(s) Kingston
	Examiner Arlen Soderquist	Group Art Unit 1743

☒ Responsive to communication(s) filed on *Jan 6, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-33* is/are pending in the application.

Of the above, claim(s) ______ is/are withdrawn from consideration.

☐ Claim(s) ______ is/are allowed.

☒ Claim(s) *1-33* is/are rejected.

☐ Claim(s) ______ is/are objected to.

☐ Claims ______ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on ______ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on ______ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) ______ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: ______ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). ______

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

Arlen Soderquist
ARLEN SODERQUIST
PRIMARY EXAMINER

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 4 there are 4 equations with the symbols used not being completely defined for three of the equations.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1 - 3, 5 - 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kingston (US 5,414,259). In the patent Kingston teaches and claims a method of speciated isotope dilution mass spectrometry. The method of determining the concentration of a specie in a sample is summarized in columns 6-7 and includes providing at least one predetermined, enriched isotope in the same speciated form as the species to be measured, spiking the sample containing the species to be measured, equilibrating the spiked species with the species to be measured, separating the different species in the sample and subsequently determining the concentration of the species to be measured by employing isotopic element specie ratios and deconvoluting any conversion of one species into another. In one embodiment, a single speciated isotope spike is employed and, in others, two or more such spikes may be employed. Column 7 lines 20-23 teach that the steps remain nearly the same when more than one species is spiked however the mathematical deconvolution is different depending on the number of spiked species and the interaction between the species. In a preferred embodiment, time resolution chromatography is used to effect separation of these species from the sample and mass spectrometer is employed in determining isotopic elemental ratios. It is also preferred that a method be employed to determine if there was conversion from one species to another. In another embodiment, spiking of the several different isotopically enriched analogs of the same specie are added at various steps in the sampling procedure and the stability and integrity of the specie with respect to these processes is evaluated by mass spectrometric measurements of the various isotopic ratios. Chemical processes, extraction methods, dissolution procedures and storage procedures are evaluated. In another

embodiment, speciated isotope dilution is used to determine the effect on species of various sample preparation methods and portions of sample preparation techniques. Extraction and separation procedures employ the technique to provide definitive evidence of accurate specie manipulation and provide for performance based measurement. Column 8 teaches an equation used in the mathematical deconvolution of the results. The equation of line 45 is taught as one used to calculate the species concentration when there is no species crossover. Column 10, beginning at line 5 and column 11 beginning at line 34, discuss the deconvolution of the results in the actual examples given. Using the equations taught will provide an indication of species interaction or crossover by changes in the isotopic ratio from the natural abundance for the different species. Column 11, lines 48-55, column 12, lines 27-32, column 13 lines 20-36 and column 14, lines 28 are reproduced below with added emphasis and correction.

> "One may determine the extent of conversion of each specie to another, and one or both may need to be corrected for conversion in different examples. The relative concentration and quantity of each isotope converted to the other can be calculated using mathematical relationships established for the specific isotopes, enrichment factors, and resolutions of the analyzing instrument."

> "The use of more than one speciated isotope provides the ability to calculate the contribution and conversion of one specie to another. This is very different from current methods wherein only the total in the final form can be determined and conversion is undesirable and unmeasurable."

> "Deconvolution of these species in the presence of each other may be determined using isotopic ratios such as, for example, CR(III) and CR(VI) species crossover by a species III to IV and vice versa shift will result in the isotope d(el)ement specie ratios being altered for each specie. Determination of the amount of crossover of one specie to another by using isotopic ratios to calculate the specie interchange becomes possible, employing the present invention."
> "Even where two isotopic spikes are not available, one spike can be used with calculation of crossover by ratio shift in one specie. An alternative is to perform the same speciated spiking experiment repeatedly but transform the isotopic spike into different species for different experiments. ***By collecting multiple measurements and doing a <u>mass balance</u> each time the entire speciation behavior mechanism can be evaluated***."

> "I. Other algorithm calculations are possible from the two components of time resolution of individual species and mass isotopic element specie ratio alterations."

This clearly shows that determining the extent of crossover was contemplated by Kingston including what kinds of mathematical equations would need to be used. Columns 12 - 16 teach various separation methods, samples, and detection methods that can be used within the scope of the invention.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kingston as applied to claims 1 - 3 and 5 - 33 above, and further in view of Chen and Ketterer or Kozerski (newly cited and applied). As taught above, column 13-14 teach the use of mass balance and other algorithms to deconvolute the results. Kingston does not teach the equation of claim 4.

In the paper Chen discusses external-source contamination during extraction-distillation in isotope-ratio analysis of soil inorganic nitrogen. The sources of contamination introduced during the extraction, distillation, and drying phases of isotope-ratio analysis of soil inorganic nitrogen (ammonium and nitrite + nitrate) were identified, and the individual amounts of contaminants were quantified by isotope dilution. The procedure involves addition of internal standard solutions of ^{15}N-labeled ammonium and nitrite to reagent blanks which are carried through each stage of the analysis at the same time as the test samples. Potassium chloride extractants, filter-papers, distillation reagents, and atmospheric ammonia all contributed to dilution of the

sample ^{15}N. Some materials tested contained sufficient contaminants to cause large errors in the determination of sample ^{15}N abundance. Both the amount and isotopic composition of contaminants can be determined by the isotope-dilution procedure, which permits the measured sample 15N abundance to be corrected for contamination. Page 51 discusses the calculations used to determine the amount of contamination. The equations are based on the mass balance principle. From the equation it is clear that the measured atomic ratio depends on the amount label in the internal standard, the amount of labeled material in the contaminant and the respective atomic ratios in the standard and the contaminant. Thus the mass balance principle includes corrections from all potential sources. Pages 53-54 discuss correcting sample for the presence of contaminant to give the uncontaminated composition. These equations also use the mass balance principle.

In the paper Ketterer teaches measurement of Tl(III/I) electron self-exchange rates using enriched stable isotope labels and inductively coupled plasma mass spectrometry. The approach for measuring electron self-exchange rate constants (k_{11}) in solution is based upon using stable isotope-labeled reactants, chemical separations, and inductively coupled plasma mass spectrometry. The technique was demonstrated for the exchange between Tl(III) and Tl(I) aquo ions in aqueous $HClO_4$. Tl(III) is prepared using ^{203}Tl-enriched Tl_2O_3 (^{203}Tl abundance, ~36%), and Tl(I) is prepared from natural abundance Tl reagents (natural ^{203}Tl abundance, 29.52%). The exchange is monitored by mixing the labeled and unlabeled reactants and performing timewise separations through selective precipitation of Tl(I) as TlBr. Isotope abundances are measured in the TlBr precipitate and Tl(III) solution phases using ICPMS with minimal sample preparation; an NIST 981 (common lead) spike was added, and the $^{208}Pb/^{206}Pb$ is measured as an internal standard to correct for mass discrimination. The self-exchange rate constant is determined from a McKay plot obtained from the ^{205}Tl abundances of either oxidation state. A k_{11} of $(1.0 \pm 0.1) \times 10^{-4}\ M^{-1}\ s^{-1}$ was obtained in 1.5 M aqueous $HClO_4$ at 25 °C. The obtained k_{11} compares favorably to a value of $1.1 \times 10^{-4}\ M^{-1}\ s^{-1}$ based upon a previously published study of this exchange reaction using radiolabeled (^{204}Tl) reactants. On page 4005 Ketterer shows the equation for the self-exchange reaction. From the equation it is clear that due to the self-exchange reaction some of the Tl(I)

species present will be from the Tl(III) isotopic species originally present in the solution. It is also clear that the Tl(III) species will likewise include Tl from the Tl(I) isotopic species originally present.

In the paper Kozerski teaches determination of aqueous Fe(III/II) electron self-exchange rates using enriched stable isotope labels, ion chromatography, and inductively coupled plasma mass spectrometry. A strategy was described for rapid online measurement of electron self-exchange rates between aqueous Fe(III) and Fe(II) in solution using stable ^{57}Fe-labeled reactants, cation chromatography, and inductively coupled plasma mass spectrometry. The self-exchange is monitored by mixing the reactants and performing time-wise separations of Fe(II) and Fe(III) ions. Separations are completed in 30-60 s using a weak phosphonic/carboxylic acid cation exchange guard column and 0.1-0.5 M aqueous $HClO_4$ eluent. The resulting time series of ^{56}Fe and ^{57}Fe chromatograms display systematic changes in isotopic abundances from which the self-exchange rate constant, k_{11}, is obtained. Two different schemes are used for mixing and sampling the reaction mixture; using a peristaltically pumped flow reactor, reaction half-lives on the order of 30 s can be monitored. A series of k_{11} results are obtained under a variety of temperature (2.0, 21.6, and 25.0 °C) and ionic strength conditions (0.10, 0.50, and 0.55 M aqueous $HClO_4$) which are congruent with three previously published radiolabeling studies for this reaction. On page 784 Kozerski shows the equations for the self-exchange reaction. From the equations it is clear that due to the self-exchange reaction, some of the Fe(II) species present will be from the Fe(III) isotopic species originally present in the solution. It is also clear that the Fe(III) species will likewise include iron from the Fe(II) isotopic species originally present.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the equation of Kingston to account for self exchange conversion of the species as taught by either Ketterer or Kozerski through the mass balance principle as taught by Chen and Kingston because as shown by Chen the mass balance principle can be used to correct for the presence of a species from different sources and one of skill in the art is capable of algebraic manipulation of mathematical equations to produce an equation which enables a desired quantity to be determined from variables that can be measured and properties which are known about a

system. In this respect Kingston also shows that one of skill in the art is expected to be able to use the mass balance principle to correct for the interconversion (self exchange) between two different oxidation state species of the same metallic ion.

6. Applicant's arguments filed January 6, 2000 have been fully considered but they are not persuasive. Relative to the anticipation by the Kingston reference, applicant is directed to the fact that the Kingston reference is directed toward the technique or **speciated** isotope dilution mass spectrometry (see title). As such it does not suffer the problems of isotope dilution mass spectrometry! Furthermore claim 1 does not require that the species are incompletely separated. It only requires that there be a separation of at least a portion of the sample. This fully encompasses taking a small portion of a larger spiked sample or separating the species in the **whole** sample! Within this scope each and every limitation of the anticipated claims are clearly and totally taught as set forth above. Applicant argued that relative to claim one the Kingston reference does not teach the ability to provide a different isotopic spike for each species with subsequent deconvolution of the species concentration while correcting for conversion. First it is pointed out that this scope includes a single species and a single isotopic spike. Second Applicant is directed to the specific quotes from Kingston listed above as evidence that a single or multiple spike was fully anticipated by Kingston. In this same manner each of the dependent limitations is fully anticipated by the Kingston reference. If applicant is trying to argue that the instant claims were not enabled in applicant's prior patent, then applicant has the burden of showing that at least claims 2-8, which deal with multiple species, were not enabled by the disclosure of the Kingston patent.

Relative to claim 4 applicant's arguments are moot in view of the new grounds of rejection. The newly cited and applied references clearly show that one of skill in the art would have recognized that application of mass balance requires an accounting of the source of a particular specie from all of its possible sources. They also show that one of ordinary skill in the art would have recognized that the interconversion or crossover of the instant application is simply the well known self exchange reaction and that an isotopic label will be converted to a

different specie through this reaction. Hence the self exchange reaction will form a source of isotopic exchange in the presence of species having different isotopic abundances.

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The cited art is directed at the use of isotopic labels and mass balance in mass spectrometric analysis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner can normally be reached Monday through Thursday and some Fridays from about 7:30 AM to about 5:00 PM.

For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Another number for official papers is (703) 305-3599. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Arlen Soderquist

February 21, 2000
ARLEN SODERQUIST
PRIMARY EXAMINER